Karolinska Institutet

Institutionen för Mikrobiologi, Tumör- och Cellbiologi

Activation and dysregulation of innate immunity in HIV-1 and HIV-2 infections

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Atrium, Nobelsväg 12B,

Måndagen den 13 december, 2010, kl 09.00

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Stockholm 2010

ABSTRACT

Toll-like receptors (TLRs) are pattern recognition receptors, expressed by antigen presenting cells (APCs) that recognize conserved molecular patterns of diverse microorganisms. TLR triggering activates APCs, leading to expression of innate effector molecules and signals that initiate adaptive immune responses. Studies have revealed that the use of TLR agonists might offer novel approaches for the development of therapeutic and prophylactic measures. Two types of human immunodeficiency virus (HIV) can cause acquired immune deficiency syndrome (AIDS): HIV-1, which is found worldwide and HIV-2, which is mostly detected in West Africa and known to be less transmissible and less pathogenic. During HIV infection, the constant battle between the virus and the immune system because of rapid viral turnover results in chronic immune activation that is thought to exhaust several compartments of the immune system. The interactions between HIV and the innate immune system remain, however, relatively unexplored.

Studies in this thesis show that the replication of both HIV-1 and HIV-2 strains can be suppressed *in vitro* by the TLR9 agonist, CpG oligodeoxynucleotide (ODN). Additionally, conjugation of ODNs with a phosphorothioate backbone to cholera toxin B subunit enhanced the anti-HIV activity. These results indicate that the use of TLR agonists might have implications for the development of new HIV intervention strategies. Furthermore, studies on the impact of HIV on TLR stimuli responsiveness reveal that both advanced HIV-1 and HIV-2 infections were associated with defective IFN-α responses after *in vitro* TLR9 stimulation. In addition, defective IL-12 expression after TLR7/8 stimulation was observed in HIV-1-infected individuals. Moreover, levels of microbial translocation, measured as concentrations of lipopolysaccharide (LPS) in plasma, were elevated in both HIV-1- and HIV-2-infected individuals with AIDS. The plasma LPS levels correlated with CD4+ T cell count and viral load, in addition to TLR responsiveness. These results suggest that alterations in innate immune responses and microbial translocation are associated with the pathogenesis of both HIV-1 and HIV-2 infections. Studies on the immunological consequences of treatment interruption- (TI) associated viremia in HIV-1-infected individuals, showed that circulating dendritic cells were reduced and that TLR stimuli responsiveness was dysregulated. Moreover, analyses of immune activation markers showed that the frequency of HLA-DR+ T cells and spontaneously released IL-12 increased during TI, whereas microbial translocation remained unaffected. Hence, innate immunity and T cell markers of immune activation are affected during HIV-1 infection even after short-term viremia, but prolonged viremia appears to be required for the detection of microbial translocation.

This thesis adds knowledge on the potential use of TLR agonists for the development of novel approaches to prevent HIV infection, but also emphasizes the need for better understanding of the role of TLR responsiveness during the pathogenesis of HIV-1 and HIV-2 infections.

ISBN 978-91-7457-153-0